Improving Early Risk Stratification in Sepsis Through Optimized Blood Culture Time-to-Positivity Modeling

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THE PROBLEM

• Sepsis: ≥1.7 million US adults/year; ≥350,000 deaths annually; the single most expensive condition in US hospital care.[1]

• Bloodstream infection (BSI) is the most lethal sepsis phenotype: ~575,000 US cases/year; case fatality 15–25% overall, higher in septic shock.[2]

• Every hour of delay to appropriate antimicrobial therapy in septic shock raises mortality by ~7.6%.[3]

THE BIOMARKER & THE GAP

• Blood culture time-to-positivity (TTP) reflects organism doubling time and bacterial burden at time of blood collection — proposed as an early prognostic biomarker.[4]

• Shorter TTP correlates with higher bacterial burden and, in pathogen-specific cohorts (e.g., *Staphylococcus aureus*), worse outcomes.[4]

• But two high-quality multicenter studies (FABLED 2021, Hamilton 2022) find TTP is NOT associated with mortality — the US/Western literature is inconsistent.[5,6]

Confounding by empiric antibiotics: high-suspicion patients receive antibiotics before culture results (mortality mitigated); low-suspicion BSIs missed empirically suffer the full delay penalty (~7.6%/h, Kumar). This bidirectional effect attenuates any unadjusted TTP–mortality signal.

TWO INTERNATIONAL SOLUTIONS

• Non-linear modeling (Ljungquist 2025, Sweden):[7] population-based cohort used restricted cubic splines to characterize the TTP–severity relationship without assuming linearity.

• mTTP correction (Tsai 2025, Taiwan):[8] adjusted TTP for transport time in 1,015 community-onset BSI patients; mTTP outperformed raw TTP for 30-day mortality prediction.

RESEARCH QUESTIONS

1. **Among adult patients with a first organism-positive blood culture episode at UC Davis Health (2019–2026), does blood culture incubation time-to-positivity (TTP), modeled with 5-knot restricted cubic splines and adjusted for age and sex, demonstrate a statistically significant non-linear independent association with hospital length of stay (primary outcome) or all-cause mortality (secondary, exploratory outcome)?**

2. **After correcting TTP for the measured pre-analytical specimen transport interval to produce modified TTP (mTTP = TTP + transport time), does prognostic performance for all-cause mortality improve relative to unadjusted TTP; and if mTTP correction fails, is this attributable to the high degree of pre-analytical transport heterogeneity at UCDH (median 120 minutes) compared with published reference cohorts (approximately 18 minutes; Tsai 2025)?**

3. **What is the distribution of Collection-to-Incubator time (CTI) for positive blood cultures at UCDH, what proportion incur delays exceeding operationally relevant thresholds (≥4 hours, ≥8 hours), and how does this burden vary across patient care settings — emergency department, intensive care unit, inpatient ward, and external/satellite facilities? What is the contribution of the midnight-to-6 AM courier gap to this distribution?**

4. **Does low blood volume per culture bottle — as a proxy for reduced bacterial inoculum — independently identify patients with higher all-cause mortality? Is the single-bottle pattern consistent with the inoculum hypothesis? (Qin 2026)**

METHODS

Design and setting: Retrospective cohort study, University of California, Davis Health (UCDH), January 2019–May 2026. Pilot data were extracted from the electronic health record via Slicer-Dicer. Confirmatory data extraction from the Electronic Antibiotic Decision Support (EADS) system is pending.

Participants: Index (first) organism-positive blood culture episode per patient (n = 8,659 first-per-patient episodes; 8,454 complete-case analytic cohort). Adults ≥18 years (n = 7,570) are the primary analysis; pediatric patients <18 years (n = 884) analyzed separately per Qin 2026. Bottle-structure subgroups (adult cohort): paired aerobic/anaerobic n = 7,443; low blood volume n = 269; single-bottle (A or N only) n = 93.

Exposures: (1) TTP — time from BACTEC™ instrument load to organism-positive flag, in hours (receipt timestamp proxy). (2) mTTP = TTP + pre-analytical transport interval (Tsai 2025 primary exposure).

Outcomes: (1) All-cause mortality — patient vital status at EHR extract (May 24, 2026); variable follow-up 0–7 years (2) Hospital length of stay (log-transformed; n = 6,675 adults).

Statistical analysis: Non-linear TTP–outcome associations modeled via 5-knot restricted cubic splines (RCS). Likelihood ratio test (LRT; 3 d.f.) vs. linear TTP specification.

Covariates: age (3-knot RCS), sex. Contamination sensitivity: three-tier exclusion (laboratory PC flag; organism-based CoNS/Micrococcus/Corynebacterium; union).

PILOT vs CONFIRMATORY DATA

Pilot (this poster) — Slicer-Dicer extract:
• TTP from receipt-to-result timestamp (proxy for true BACTEC instrument-load).
• Mortality = vital status at extract (May 2026); follow-up 0–7 yr; not 30-day.
• Contamination: single-flag heuristic (not paired-set adjudicated).
• No severity scores, no antibiotic timing.

Confirmatory — EADS extraction (pending) will provide:
• Verified BACTEC load timestamps (true TTP, true mTTP).
• Registry-linked 30-day all-cause mortality.
• Per-bottle volumes for covariate-adjusted inoculum analysis.
• SOFA components, lactate, procalcitonin, CRP.
• Paired-set contamination adjudication.

→ The pilot establishes pipeline + methods; EADS will refine every endpoint and adjustment.

Other caveats: TTP–mortality attenuated after laboratory-flagged contamination exclusion (p=0.12–0.20 across three-tier sensitivity; PC-flag excl. p=0.20, organism-based excl. p=0.12); TTP–LOS directionally robust but also attenuated (p=0.077–0.17). Unadjusted courier-gap mortality comparison is acuity-confounded (fast-transport cultures select for sicker patients on STAT orders).

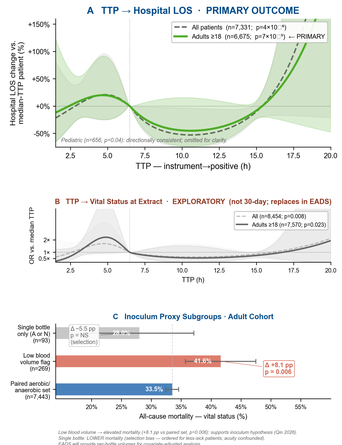
TRANSPORT WORKFLOW (CTI)

UCDH median CTI is ~7× longer than published international reference cohorts.

Median CTI: **120 min**
IQR 86–184 min · Mean 169 min · P95 454 min

Published reference: **~18 min**
Tsai 2025 cohort (Taiwan)

Cultures positive by 8 h: **28.2%**
logistical status quo prior to 2026 intervention
HVC-QI gap: midnight–6 AM courier blackout delays ~15% of cultures by 4–6 h



PRIMARY FINDING

Adult cohort, n = 7,570

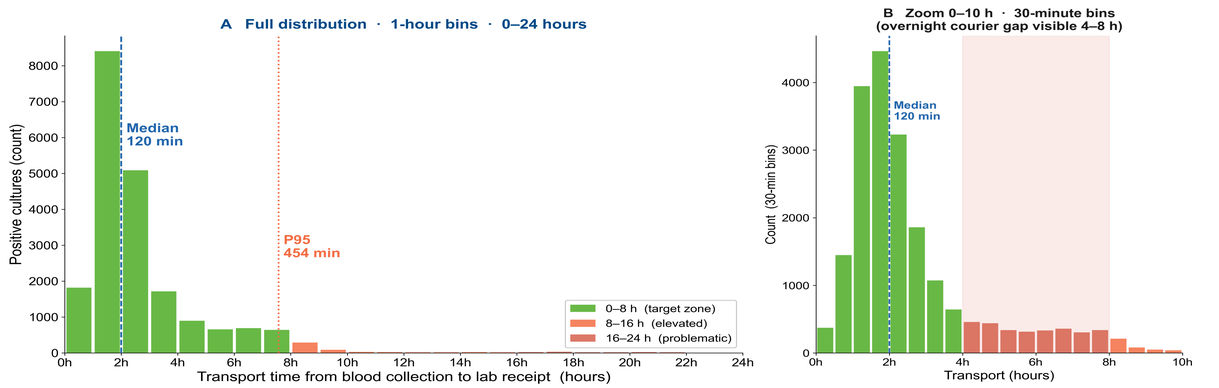
TTP → log LOS (PRIMARY)
LRT $\chi^2(3) = 21.79$, $p = 7.2\times10^{-5}$
n = 6,675; $R^2 = 0.041$
Total cohort: $p = 4\times10^{-6}$ (robust)

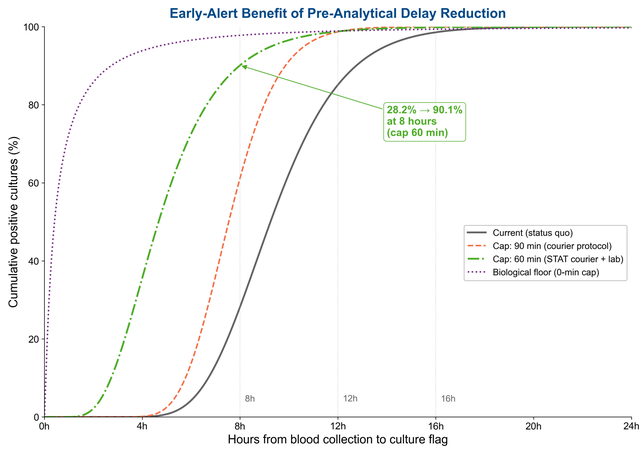
TTP → mortality (EXPLORATORY)
LRT $\chi^2(3) = 9.51$, p = 0.023
n = 7,570; events = 2,497; C = 0.64
* Endpoint = vital status at EHR extract (May 2026); not 30-day.

ICU SUBGROUP — strongest signal
TTP→mortality: $\chi^2(3)=23.9$, p<0.001 (n=976, 41% mort.)

INOCULUM (Panel C)
Low-vol flag: +8.1 pp (p=0.006)
Single-bottle: -5.5 pp (NS; acuity-confounded)

Pre-Analytical Transport Delay Distribution · n = 20,710 positive cultures, 2019–2026





CONCLUSIONS

» Non-linear TTP–hospital LOS is the primary robust finding (total cohort p = 4×10^{-6}; adult primary analysis p = 7×10^{-6}), driven by inpatient strata and consistent across sex and racial/ethnic groups.

» The strongest TTP–mortality association is in the intensive care unit subgroup (p < 0.001, n = 976), where earlier TTP results would be most clinically actionable for antibiotic escalation and de-escalation. The whole-cohort mortality finding is exploratory (vital-status endpoint; will be resolved in EADS).

» Modified TTP (mTTP) correction failed to improve prognostic performance at UCDH: CTI is approximately 7-fold longer than the Tsai 2025 reference setting (median 120 min vs. ~18 min), adding non-biological heterogeneity that attenuates the mTTP–mortality signal (p = 0.325).

» Low blood volume specimens had higher all-cause mortality (+8.1 pp, p = 0.006), supporting the inoculum hypothesis (Qin 2026). Single-bottle cultures had lower mortality than paired sets (−5.5 pp, NS), consistent with acuity-selection confounding rather than a biological inoculum effect — underscoring the need for per-bottle volumes in EADS.

» The midnight-to-6 AM courier gap generates an accumulation of 4–8 h CTI delays (visible in Panel B, Figure A). Targeted overnight courier runs or STAT prioritization would directly reduce this zone and advance blood culture positivity flagging by up to 6 hours.

NEXT STEPS

• EADS extraction: verified BACTEC timestamps, registry-linked 30-day mortality, per-bottle volumes for inoculum-adjusted analysis.

• Severity covariate adjustment: SOFA score, serum lactate, procalcitonin.

• Overnight courier pilot (on-going, starting in early 2026): quantify the CTI reduction for midnight–6 AM draws at UCDH

RESULTS — ADULT COHORT

n = 7,570 adults · LOS subset n = 6,675 · Pediatric n = 884 (separate)

Model performance (primary analysis)

Exposure	Outcome	p (non-linear)	C / R^2
TTP (inst.→pos.)	**log(LOS)**	**7.2×10^{-6} PRIMARY**	**R^2 = 0.041**
TTP (inst.→pos.)	Mortality †	0.023 exploratory	C = 0.64
mTTP (coll.→pos.)	Mortality †	0.325 null	C = 0.65

† Mortality endpoint = vital status at EHR extract (May 2026); variable follow-up 0–7 yr. NOT 30-day. Will be replaced in EADS.

SUBGROUP FINDINGS

- **Adult Low blood volume cohort (n=269): 41.6% mortality vs. paired-set reference (n=7,443) 33.5% (+8.1 percentage points; χ^2=7.72, p=0.006). Supports the inoculum hypothesis: inadequate specimen volume may reflect harder-to-phlebotomize patients or true under-sampling of the bacteremic inoculum.**
- Single bottle only (A or N; n=93): 28.0% mortality vs. 33.5% paired (−5.5 pp; p = NS). Counter to the inoculum hypothesis. Most likely explanation: single-bottle cultures are ordered preferentially for less-critically ill patients (acuity selection bias), not driven by reduced inoculum. EADS per-bottle volumes will enable adjusted analysis.
- Intensive care unit (ICU) subgroup (n=976): 41.0% all-cause mortality vs. 30.3% non-ICU. TTP–mortality association strongest in ICU (LRT p<0.001, χ^2=23.9).
- Pediatric cohort (n=884): TTP–hospital LOS directionally consistent with adults (LRT p=0.04). Bottle structure subgrouping is clinically distinct: recommended blood volume is weight-based (minimum 1–3 mL/kg), making standard adult paired-set criteria non-applicable. EADS will provide weight-adjusted per-bottle volumes for pediatric inoculum analysis.

BY CARE SETTING

Adult cohort mortality and TTP outcome p-values per stratum

Setting	n	Mort%	Med LOS	TTP→Mort p	TTP→LOS p
Emergency (ED)	4,138	29.7%	6 d	0.47	0.07
ICU	**976**	**41.0%**	**25 d**	**<0.001 ★**	**0.05**
Other inpatient	3,545	31.4%	17 d	0.18	<0.001 ★

★ ICU: TTP→mortality is the strongest subgroup signal. Other inpatient: TTP→LOS is the strongest subgroup signal.

EQUITY — OUTCOME MODEL (TTP → Hospital LOS, adult cohort)

5-knot restricted cubic spline TTP to linear TTP specification, adjusted for age and sex. All strata: longer TTP associated with longer hospital LOS.

Stratum	n (LOS subset)	LRT $\chi^2(3)$	p value	Interpretation
Male	4,186	21.8	<0.001	Non-linear TTP–LOS confirmed; consistent with primary adult model
Female	2,677	11.1	0.011	Non-linear TTP–LOS confirmed; consistent with primary adult model
White	3,408	13.6	0.004	Non-linear TTP–LOS confirmed; consistent with primary adult model
Other / Unknown	1,864	14.7	0.002	Non-linear TTP–LOS confirmed; consistent with primary adult model
Asian	637	7.7	0.053	Borderline significance (p = 0.053); statistical power limited
Black / African American	954	5.1	0.17	Directionally consistent; not significant, limited stratum power (n = 954)

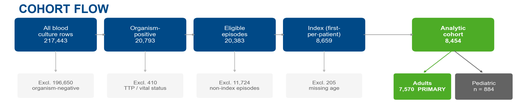
EQUITY — PRE-ANALYTICAL TRANSPORT BY SETTING

Collection → lab receipt, all cultures 2019–2026 (n = 207,630 with valid timestamp)

Setting	N	Median	IQR	≥4 h (%)
ED	86,143	110 min	80–162 min	14%
ICU (adult)	26,834	112 min	83–166 min	15%
Inpatient ward	69,605	127 min	92–184 min	16%
PICU / NICU	8,555	118 min	87–176 min	15%
External/satellite	**10,672**	**315 min**	**201–533 min**	**67%**

Within-hospital settings comparable (110–127 min). External/satellite (Vibra, dialysis, regional labs): 315 min median, 3× longer, 67% ≥4 h. These patients are older and have higher comorbidities. Satellite courier optimization is the highest-leverage workflow target.

COHORT FLOW



DEMOGRAPHICS (Table 1)

Variable	Adults (n 7,570)	Pediatric (n 884)
Age, yr median [IQR]	62 [48–72]	1 [0–9]
Male sex	4,612 (60.9%)	525 (59.4%)
Race: White	3,755 (49.6%)	—
Race: Black / African American	1,045 (13.8%)	—
Race: Asian	659 (8.7%)	—
Race: Other / Unknown	2,111 (27.9%)	—
Mortality †	2,497 (33.0%)	125 (14.1%)
Hospital LOS ‡ med [IQR]	10 [5–23] d	—

† Vital status at EHR extract (May 2026); variable follow-up 0–7 yr; ‡ LOS available for 6,675 of 7,570 adults (88.2%).

mTTP — SUPPLEMENTARY

mTTP (collection→positive) null for mortality (adult p=0.325). Heterogeneous transport drowns the mTTP signal.

Measure	LRT p	Direction	Interpretation
TTP (incubation)	**0.023**	**Non-linear**	**Shorter TTP → longer LOS / higher mortality; primary robust finding**
mTTP (coll.→pos.)	0.325	Null	UCDH CTI adds variance (120 min med. vs. ref ~18 min; Tsai 2025)

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